EPA Hazard Characterization of Non-Cancer Effects of Libby Asbestos

Strengths

- LPT is a reasonable critical endpoint - structural abnormality, associated with reduced lung function, risk factor for other asbestos-related outcomes
- Animal data showing LA causes non-cancer effects in rodents (lung fibrosis)

Weaknesses

- Justification of LPT as adverse effect can be stronger
- Insufficient MOA data
- RfC based on subgroup data from single study
- RfC could drive risk more than the cancer IUR
- Discussion of smoking issues in text not adequate

How do we consider early life exposures?

- Evaluate other environmental amphibole exposures / studies – especially children (some already in susceptibility section)
- Evaluate animal studies on age-specific effects to other amphiboles

Relevance of other literature related to amphiboles

- Literature on other amphiboles should be included, particularly inhalation studies in rodents
- Abundance of MOA data on other amphiboles
- Other populations exposed to amphiboles environmentally
- Other literature related to the significance of pleural plaques (effect on lung function, risk of other asbestos-related diseases)

Recommendations for EPA

- Strengthen rationale for RfC
  - External validation by comparison with other amphibole-exposed cohorts for which there are exposure data (e.g., Wittenoon) and other Libby Asbestos-exposed cohorts, including MN
  - Address small sample size concerns
  - Analysis combining all radiographic non-cancer abnormalities
- Consider literature on other amphiboles –
  - Animal studies – revise conclusion to indicate that MOA of LA is likely to be similar to the MOA for other amphiboles
  - Community exposures to other amphiboles (e.g., Wittenoon)

Summary from Reference Concentration Group Strengths and Weakness of EPA Report

- Strengths
  - Marysville subcohort currently the best cohort
    - Highly relevant population with validated outcome
    - No downward extrapolation
    - Exposures were measured
  - Thoughtful approach to modeling
  - Groundbreaking for non-malignant endpoint
- Weaknesses
  - RfC based on single, small cohort
  - Limited exposure duration

Recommendations

- Accept Marysville subcohort as primary tool for RfC
- Fine tune the RfC estimate based on this subcohort
  - Investigate alternative exposure metrics
  - Investigate alternative models
  - Improve justification of BMR, BMCL selection, and uncertainty factors
- Substantiate RfC with other cohorts
  - Revise full Marysville cohort analysis
  - Compare to other selected studies

Role of Early Life Exposures

- EPA currently lacks the evidence/data to adjust the RfC, despite our concern about childhood exposure
- Intraspecies uncertainty factor provides some protection

Relevant Amphibole Literature

- Papers supporting RfC
  - Larson *et al*. 2012 (Libby workers)
  - Adgate *et al.* 2011 (Minneapolis)
    - Exposures are estimates, not measurements
  - Alexander *et al.* 2012 (Minneapolis)
- Separating out TSFE
  - Paris *et al* 2008
    - Exposure assessment of limited value?
- Justification of a fixed plateau (85%)
  - Lilis *et al.* 1991 (Radiographic/smoking)

Summary from Hazard Identification of Cancer Weight of Evidence Group

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Bottom Line Conclusion

- *There was consensus agreement with EPA's conclusion that Libby amphibole is "Carcinogenic to Humans" by the inhaled route. This is based on convincing epidemiological evidence of a causal association between Libby amphibole exposure and lung cancer and mesothelioma. The epidemiologic data were strong and provided a clear indication of a cancer hazard from Libby amphibole. Animal data and mechanistic information, while limited, do provide biological plausibility and are consistent with findings with other amphibole fibers.*

Strengths of EPA Draft Document

- Report is comprehensive and balanced and lucidly written for the most part
- Uncertainties well considered
- Appropriate focus on Libby amphibole information and consideration of other information relevant to Libby material (ie tremolite)
- Justification in splitting the cohort into a sub-cohort with good exposure history
- Good diligence in getting mesothelioma numbers ascertained
- Good coverage of literature up to deadline

Weaknesses of EPA Draft Document

- Discussion of Libby amphibole versus information on other amphiboles could be strengthened
- Sections are less concise than they should be and included extraneous material
- Could use more tabular comparison to 1986 Asbestos document (previous gold standard)
- Some inconsistency in writing (example section 3 vs section 6 material on toxicokinetics)
- Some sections are repetitive (5.4.4 and 5.4.5)

Recommendations to EPA

- **Section 4.2 should start with discussion of relevance of routes of exposure and then discuss inhalation data followed by other, less relevant routes.**
- **Add discussion of known amphibole fiber toxicity determinants (dose, durability, dimension, surface chemistry).**
- **Add some additional causes of death (eg. COPD) to full- and sub-cohorts (Tables 5-6, 5-8)**

Modes of Action (MOA)

- Consensus agreement with EPA conclusion that there are insufficient data to ascribe a particular MOA. Multiple modes are highly likely.
- Most toxicology studies not by relevant routes and are too short to show relevant chronic endpoints.
- There are insufficient data to support the claim made in Section 4.6.2.2. that weight of evidence doesn't support mutagenic mode of action for Libby amphibole.

Guidance Concerning Early Lifestage Susceptibility

- **There is inconsistency in the tone of the conclusions in Section 4.7.1.1 and in Section 6.3.3 to support or refute early lifestage susceptibility**
- **Encourage the continued monitoring of relevant Libby residents for early onset asbestos associated diseases**
- **Re-look at other models that might be a better fit for determination of early lifestage susceptibilty**

IUR

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Strengths and weaknesses

- Herculean effort
- Documentation clear and mostly complete
- Highly focused on data relevant to LAA
- Basic uncertainty analysis via sensitivity methods

- Constrained by specificity to Libby sub-cohort
- Overly focused on models that fit data well
- Used generic policy, rather than broader amphibole asbestos literature for early-life exposures
- Sensitivity analyses not integrated

Recommendations

- Characterize model uncertainty as the range of performances from a *rodeo* of models
  - Include models that are selected by considerations other than fit alone (e.g., other epi evidence)
  - Present fit to data graphically with good range of fitted curves
- Review/justify independence assumption
  - Or use methods that don't require the assumption
- Analyze full Libby cohort using bounded exposures
  - 2/3 of the mortalities, although maybe only 5% of info

More recommendations: Strengthen Uncertainty Analysis

- Objective: comprehensive uncertainty analysis
  - Quantitatively characterize major uncertainties, at least using interval ranges
  - Use an integrated (single) sensitivity analysis, to project all uncertainties simultaneously (e.g. Monte Carlo methods, info gap analysis)
- Pragmatic: individual sensitivity analysis
  - Be explicit about amount of uncertainty accounted for by guidance-driven assumptions
  - Give quantitative implications of key sources of uncertainty for IUR

Advice on early-life exposures

- Use the broader amphibole asbestos literature
- Model mesothelioma risk for early life exposure (e.g., Nicholson, 1986 EPA/600-8-84/003F)
- Evaluate and discuss the evidence regarding related use of adjustment factors for lung cancer